REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

The 35 U.S.C. §112 Rejection

Claims 11-17, 19-21, 23, 24, 27-30, 40-45 and 53-56 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner contended that "the claims are directed to a method of genetically manipulating $CD40^+$ immune cells in a human subject, for suppressing immune response.... for the treatment of diseases including all types of cancer, infectious diseases, transplantation rejection, and autoimmune diseases". Applicants respectfully disagree.

Claims 11-16, 27-28 are drawn to methods of using the gene delivery system of the instant invention to genetically modify

instant invention can both mediate gene transfer to and cause maturation of $CD40^+$ immune cells. The claimed methods of gene transfer may be useful in individuals having cancer, infectious diseases, transplantation rejection, or autoimmune diseases. Applicants reiterate that the claims are drawn to methods of gene transfer. The claims are not drawn to and have not recited treatment of diseases including all types of cancer, infectious diseases, transplantation rejection, and autoimmune diseases.

The present application discloses enhanced gene transfer to $CD40^+$ cells by retargeting the adenovirus to CD40. CD40-targeted virus demonstrated both dramatic and quantitative improvements in gene transfer compared to untargeted virus (Examples 1, 3-4; Declaration of Dr. David T. Curiel, enclosed). The claimed gene delivery systems also induce maturation of $CD40^+$ cells as manifested by phenotypic and functional criteria (Examples 1, 3; Declaration of Dr. David T. Curiel). Therefore, Applicants submit that the scope of claims 11-16 is commensurate with the enablement provided in the specification.

Claims 17, 19-21, 23, 24, 29-30, 40-45 and 53-56 are [illegible] CD40 targeted adenoviral vectors of

the instant invention to enhance the vaccination potential of dendritic cells. As discussed above, the CD40-targeted adenoviral vectors of the instant invention mediate both gene transfer to and cause maturation of $CD40^+$ dendritic cells. Consequently, dendritic cells modified by the CD40-targeted adenoviral vectors of the instant invention have increased vaccination potential. This is supported by the fact that human dendritic cells infected by untargeted adenovirus were found to acquire a T cell non-stimulatory phenotype over time, whereas data presented in the attached Declaration of Dr. Curiel indicate that CD40 targeting of adenovirus ensure the ability of the transduced dendritic cells to stimulate T cells for at least up to a week after transduction.

The claimed methods of increasing the functions of dendritic cells are applicable in individuals having cancer, infectious diseases, transplantation rejection, or autoimmune diseases. In contrast to the Examiner's assertion, the claimed methods are not drawn to and have not recited treatment of diseases including all types of cancer, infectious diseases, transplantation rejection, and autoimmune diseases.

The Examiner rejected the claimed methods by citing references that indicate the efficacy of DNA vaccines still needs to be improved and there is no effective gene transfer approach for the treatment of CF lung disease at present. However, the claimed methods are not drawn to the efficacy of DNA vaccines or gene therapy for CF lung disease; nor does the success of the instant invention depend on the efficacy of DNA vaccines or gene therapy for CF lung disease.

The present specification employs a HPV-induced tumor model and an adenovirus vector, AdE7, that expresses a functionally mutated gene for the E7 antigen of HPV to establish the immunization efficacy of adenoviral modified dendritic cells. The advantage of CD40-targeting of adenovirus in a vaccination context was demonstrated in a dose response curve comparing untargeted (AdE7) and CD40-targeted AdE7 (40AdE7) vectors (Example 3). At a dose of 12,000 dendritic cells, for example, tumors developed in animals vaccinated with dendritic cells transduced by untargeted AdE7 but not in animals immunized with CD40AdE7 (Figure 13). Of note among the tumors that did develop in mice in the lower dosage classes of E7 modified dendritic cells, the kinetics of tumor growth

that features of CD40-targeted adenovirus, namely increased gene transfer and induced maturation of dendritic cells, translate into an advantage for vaccination.

The Examiner also cited references that contend therapies that prevent diabetes in rodent models have not been efficacious in human, and clinical trials for tumor immunotherapy have been somewhat disappointing in human. However, as discussed above, the claimed methods are not drawn to treatment for autoimmune diseases or tumor immunotherapy; rather the claimed methods are drawn to increasing the vaccination potential of dendritic cells by CD40-targeted adenoviral vectors that deliver foreign genes to and activate maturation of dendritic cells.

According to the Examiner, the specification is non-enabling because the "specification fails to demonstrate that any therapeutic effect was achieved in any recited disease in humans by the CD40 targeted adenoviral vector." Applicants respectfully submit a demonstration of a "therapeutic effect" in "humans" is not a requirement under 35 U.S.C. §112, first paragraph.

In view of the above remarks, Applicants submit that the

have reasonable correlation to the scope of the enablement provided by the specification. Accordingly, Applicants respectfully request that the rejection of claims 11-17, 19-21, 23, 24, 27-30, 40-45 and 53-56 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 1 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 1 has been amended to recite a recombinant adenovirus and a first antibody fused to a second antibody. Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 11, 14, 17, 21, 40, 43, 53 and 54 were rejected under 35 U.S.C. §112, second paragraph, for reciting "such treatment". The claims have been amended to delete the phrase. Accordingly, Applicants request that the rejection of claims 11, 14, 17, 21, 40, 43, 53 and 54 under 35 U.S.C. §112, second paragraph, be withdrawn.

Double Patenting

Claims 1, 3-10, 25, 26, 31, 33-37 and 46-50 were rejected under the judicially created doctrine of obviousness-type double

patenting as being unpatentable over claims 1-6 of U.S. Patent 6,284,742. The rejection is respectfully traversed.

Claims 31 and 46 are drawn to genetically modified adenoviruses having a fiber protein comprising CD40 ligand. In one embodiment, the fiber shaft of the fiber protein is further replaced by bacteriophage T4 fibritin protein. Example 7 of the instant specification teaches the making of these modified adenoviruses. Firstly, a fiber chimera comprising a CD40L globular domain and a bacteriophage fibritin which replaces the natural fiber shaft was disclosed. Alternativley, only the fiber knob was replaced with the globular domain of CD40L (Example 7).

In contrast, claims 1-6 of U.S. Patent 6,284,742 only claim a gene delivery system comprising an adenovirus and a bispecific antibody that targets the adenovirus to CD40. U.S. Patent 6,284,742 did not teach or suggest a genetically modified adenovirus having a fiber protein comprising CD40 ligand as claimed herein. Hence, claims 31, 33-37 and 46-50 of the instant application are not co-extensive with claims 1-6 of U.S. Patent 6,284,742. Accordingly, Applicants respectfully request that the double patenting rejection of claims 31, 33-37 and 46-50 be withdrawn.

This is intended to be a complete response to the Office Action mailed March 21, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: July 10, 2002

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391
badler1@houston.rr.com

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (twice amended) A gene delivery system for CD40$^+$ immune cells, comprising:

(a) ~~an~~ a recombinant adenovirus; and

(b) a component recognizing CD40 antigen comprising a first antibody, or antigen-binding fragment thereof, that binds to a fiber-knob protein of said adenovirus, wherein said first antibody or antigen-binding fragment thereof is fused ~~attached~~ to a second antibody, or antigen-binding fragment thereof, that binds to CD40 antigen.

Claim 11 has been amended as follows:

11. (twice amended) A method for genetically manipulating CD40$^+$ immune cells in an individual ~~in need of such treatment~~, comprising the step of:

administering the gene delivery system of claim 1 to said individual, wherein said gene delivery system mediates gene transduction and causes maturation of said immune cells.

Claim 14 has been amended as follows:

14. (twice amended) A method for genetically manipulating $CD40^+$ immune cells in an individual ~~in need of such~~ treatment, comprising the step of:

administering the gene delivery system of claim 6 to said individual, wherein said gene delivery system mediates gene transduction and causes maturation of said immune cells.

Claim 17 has been amended as follows:

17. (twice amended) A method for enhancing dendritic cell-based vaccination in an individual ~~in need of such treatment~~, comprising the step of:

administering the gene delivery system of claim 1 to said individual, wherein said gene delivery system increases vaccination efficacy of $CD40^+$ dendritic cells in said individual.

Claim 21 has been amended as follows:

21. (twice amended) A method for enhancing dendritic cell-based vaccination in an individual in need of such treatment, comprising the step of:

administering the gene delivery system of claim 6 to said individual, wherein said gene delivery system increases vaccination efficacy of $CD40^+$ dendritic cells in said individual.

Claim 40 has been amended as follows:

40. (twice amended) A method for enhancing dendritic cell-based vaccination in an individual ~~in need of such treatment~~, comprising the step of:

administering the gene delivery system of claim 34 to said individual, wherein said gene delivery system increases vaccination efficacy of $CD40^+$ dendritic cells in said individual.

Claim 43 has been amended as follows:

43. (twice amended) A method for enhancing dendritic cell-based vaccination in an individual ~~in need of such treatment~~, comprising the step of:

administering the gene delivery system of claim 38 to said individual, wherein said gene delivery system increases vaccination efficacy of $CD40^+$ dendritic cells in said individual.

Claim 53 has been amended as follows:

53. (twice amended) A method for enhancing dendritic cell-based vaccination in an individual ~~in need of such treatment~~, comprising the step of:

administering the gene delivery system of claim 47 to said individual, wherein said gene delivery system increases vaccination efficacy of $CD40^+$ dendritic cells in said individual.

Claim 55 has been amended as follows:

55. (twice amended) A method for enhancing dendritic cell-based vaccination in an individual ~~in need of such treatment~~, comprising the step of:

administering the gene delivery system of claim 51 to said individual, wherein said gene delivery system increases vaccination efficacy of $CD40^+$ dendritic cells in said individual.